REMARKS

The rejection of the claims under 35 U.S.C. §112, first paragraph, is obviated in part by amendment and traversed in part.

The claims have been amended to clarify and/or clearly define the terms, which the Examiner has held to be not enabled. With regard to the "proviso" pointed out by the Examiner (paper number 6, page 7, line 8), Applicants submit that this proviso was inserted in the PCT stage of the present application to clearly distinguish the compounds of the present invention from the compounds disclosed in WO 93/13128, WO 98/49144, and WO 99/32446. Specifically, dihydropyrimidine compounds having general formula (1), wherein B_1 represents a lower alkylcarbonyl group only when L represents an oxygen atom, Y represents an interatomic bond and E represents a hydrogen atom, are not disclosed or suggested in these references, much less the high N-type calcium inhibiting effect of these compounds.a

Further, the present invention is based, in part, on the discovery that the dihydropyridine derivatives described in the present application function as antagonists towards N-type calcium channels. Applicants submit herewith several articles from the literature which demonstrate that N-type calcium channel antagonist activity is associated with treating the claimed disease states.

Cox et al., *Exp. Opin. Ther. Patents* 1998, 8(10), pp. 1237-1250 demonstrate the relationship between N-type calcium channel anatgonist function and encephalopathies caused by ischemia in the acute phase after the onset of cerebral infarction, cerebral hemorrhage, sharp pain caused by thromoangitis obliterans, pain after an operation, migraine,

and visceral pain.

The following publications demonstrate that Alzheimer's disease, AIDS related dementia, and Parkinson's disease are caused by glutamic acid: (1) Neurochem. Int. 1994, Sept., 25(3), pp. 203-219; (2) Neurosci. Biobehav. Rev. 1997, Jul., 21(4), p. 393-400; and (3) Arch. Neurol. 1991, Dec., 48(12), pp.1281-4. Since it is known that N-type calcium channel antagonists can inhibit the release of glutamic acid, such compounds can be used to treat these diseases. Similarly, glutamic acid is also causative for progressive neurodegenerative diseases.

The following references relate to neuropathy caused by head injury: (1) Brain Res. 1999, Jan. 30, 817(1-2), pp. 84-92; (2) Brain Res. 1990, Dec. 24, 537(1-2), pp. 256-262; and (3) Brain Res. 1998, Aug. 10, 801(1-2), pp. 50-58. This disease is caused by lack of oxygen and the like and, therefore, the relationship between this disease and N-type calcium antagonist can be explained in the same manner as cerebral infarction. These publications show that N-type calcium channel antagonists can be used to treat this condition.

The following references relate to drug addiction withdrawal symptoms: (1) Eur. J. Pharmacol. 1992, Jul. 21, 218(1), pp. 75-81 and (2) J. Pharmacol. Exp. Ther. 1998, Sep., 286(3), pp. 1171-1176. These publications demonstrate that an N-type calcium channel antagonist can be used to treat this condition.

Based on the foregoing, it is clear that N-type calcium channel antagonists can be used to treat the disease conditions recited in the present claims. Accordingly, the claims are enabled within the meaning of 35 U.S.C. §112, first paragraph. Withdrawal of this ground of rejection is respectfully requested.

As part of the rejection of the claims under 35 U.S.C. §112, first paragraph, the Office required restriction in the present application by the election of a single disclosed Species of the diseases disclosed in Claims 31-39. The Examiner bases this restriction on the assertion that the claims list "may diseases in a vague manner that are notoriously difficult to treat; that would require considerable proof." However, Applicants believe that, in view of the foregoing, the claims as presented herein do meet the "specific utility" standard. As such, Applicants kindly request that the Examiner not needlessly restrict their invention to only one disease and/or utility, when they are clearly entitled to the full scope as presented and enabled in the present application.

However, in order to be full responsive to the outstanding Office Action, Applicants elect, with traverse, the diseases recited in Claim 38, for further prosecution. Claims 33 and 38 read on the elected species.

Applicants make no statement regarding the patentable distinctness of the species, but note that for restriction to be proper, there must be a patentable difference between the species as claimed. MPEP §808.01(a). Applicants respectfully traverse the Election of Species Requirement on the grounds that the Office has not provided any reasons or examples to support a conclusion that the species are indeed patentably distinct. Accordingly, Applicants respectfully submit that the restriction is improper, and Applicants' election of species is for examination purposes only.

Moreover, the MPEP in §803 states as follows:

> "If the search and examination of an entire application can be made without a serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions."

Applicants respectfully submit that a search of all the claims would not impose a serious burden on the Office.

Finally, with respect to the elected species, Applicants respectfully submit that, should the elected species be found allowable, the Office should expand its search to the non-elected species.

Accordingly, and for the reasons presented above, Applicants submit that the Office has failed to meet the burden necessary in order to sustain the Election of Species Requirement. Withdrawal of the Election of Species Requirement is respectfully requested.

Applicants note that consideration of the Information Disclosure Statements submitted on April 22, 2002 and May 29, 2002, has not been acknowledged. Applicant request acknowledgement of the same by providing them with an initialed copy of the Form PTO-1449 submitted on April 22, 2002 and May 29, 2002, at the Examiner's earliest convenience. A copy of Form PTO-1449, along with a copy of the date-stamped filing receipt evidencing timely filing thereof, is attached herewith for the Examiner's convenience for each of these Information Disclosure Statements.

Applicants submit that the application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

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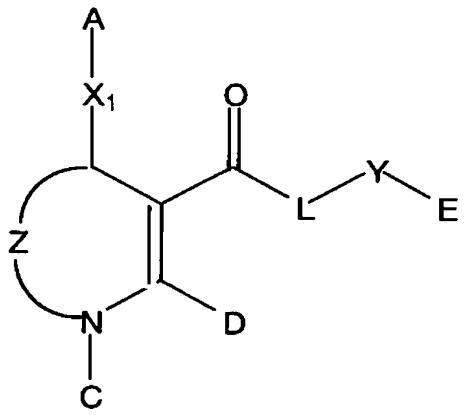
IN THE CLAIMS

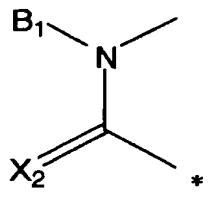
Please amend the claims as follows:

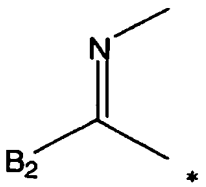
--1. (Twice Amended) A dihydropyrimidine compound of the following formula (1), a tautomer thereof or a pharmaceutically acceptable salt thereof:



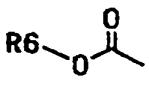
(1)

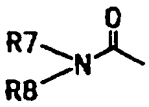
wherein Z represents a group of the following formula (Z_1) or (Z_2), which is bonded to the nitrogen atom at a symbol "*".

(Z1) 

(Z2) 

wherein B_1 represents hydrogen atom, a lower alkyl group which optionally contains a hetero atom in the chain thereof, a lower alkylcarbonyl group [(], only when L represents oxygen atom, Y represents an interatomic bond and E represents hydrogen atom[)], an [aryl-lower alkyl] benzyl group, a [heteroaryl-lower alkyl] pyridylmethyl group, a hydroxy-lower alkyl group, a halogeno-lower alkyl group, an amino-lower alkyl group, a carboxy-lower alkyl group, a lower alkyloxycarbonyl-lower alkyl group or a group of the following formula (3) or (4):

(3) 

(4) 

wherein R^6 to R^8 each represent hydrogen atom, a linear, branched or cyclic, saturated or unsaturated hydrocarbon group having 1 to 6 carbon atoms, a substituted or unsubstituted phenyl [aryl] group, a substituted or unsubstituted heteroaryl group, wherein said heteroaryl group is selected from the group consisting of a pyridyl, a furyl, and a thienyl, a hydroxy-lower alkyl group, a hydroxy-lower alkenyl group, a halogeno-lower alkyl group, a halogeno-

lower alkenyl group, an amino-lower alkyl group, an amino-lower alkenyl group, a carboxy-lower alkyl group, a carboxy-lower alkenyl group, a [substituted or unsubstituted aryl-lower alkyl] benzyl, a 3-phenylpropyl group, a [substituted or unsubstituted aryl-lower alkenyl] 3-phenyl-2-propane-1-yl group, a [substituted or unsubstituted diaryl-lower alkyl] 3,3-diphenylpropyl group, a [substituted or unsubstituted heteroaryl-lower alkyl] 3-(pyridine-2-yl) propyl group, a [substituted or unsubstituted heteroaryl-lower alkenyl] 3-(pyridine-2-yl)-2-propene-1-yl group, a cyano-lower alkyl group or a cyano-lower alkenyl group, [and] the chains of R^6 to R^8 optionally contain a hetero atom and R^7 and R^8 may together form a ring selected from the group consisting of piperidine-l-yl, piperidine-4-yl, pyrrolidine-1-yl, pyrrolidine-3-yl, piperidinone-1-yl, pyrrolidizone-1-yl, piperazine-1-yl and morpholine-4-yl, with the proviso that when R^6 to R^8 each represent a linear, branched or cyclic, saturated or unsaturated hydrocarbon group having 1 to 6 carbon atoms, a substituted or unsubstituted [aryl] phenyl group, a hydroxy-lower alkyl group, a hydroxy-lower alkenyl group, a halogeno-lower alkyl group, a halogeno-lower alkenyl group, a carboxy-lower alkyl group, a carboxy-lower alkenyl group, a [substituted or unsubstituted aryl-lower alkyl] benzyl, a 3-phenylpropyl group, a [substituted or unsubstituted aryl-lower alkenyl] 3-phenyl-2-propane-1-yl group, a [substituted or unsubstituted heteroaryl-lower alkyl] 3-(pyridine-2-yl) propyl group, or, a [substituted or unsubstituted heteroaryl-lower alkenyl] 3-(pyridine-2-yl)-2-propene-l-yl group wherein the substituents in the substituted phenyl, pyridyl, furyl and thienyl groups are those described later with reference to R^1 to R^5 in general formula (2), L must be oxygen atom, Y must be an interatomic bond and E must be hydrogen atom;

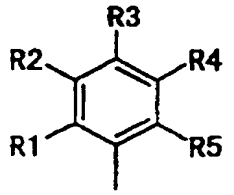
B_2 represents an amino group, a lower alkyl group [which optionally contains a hetero

atom in the chain thereof], a lower alkylamino group, a lower alkylthio group, [an aryl-lower alkyl] benzyl group, a [heteroaryl-lower alkyl group] pyridylmethyl, a hydroxy-lower alkyl group, a halogeno-lower alkyl group, a substituted or unsubstituted [aryl] phenyl group or a substituted or unsubstituted heteroaryl group, wherein said heteroaryl group is selected from the group consisting of a pyridyl group, a furyl group, and a thienyl group and wherein the substituents in the substituted phenyl, pyridyl, furyl and thienyl groups are halogen atoms, hydroxyl group, carboxyl group, amino group, cyano group, nitro groups, lower alkyl groups, lower alkoxyl groups, halogeno-lower alkyl groups, hydroxyl-lower alkyl groups and lower-alkoxycarbonyl groups;

X_2 represents oxygen atom or sulfur atom;

A represents a group of the following formula (2), or a substituted or unsubstituted l-naphthyl, 2-naphthyl, indole-2-yl, indole-3-yl, thiophene-3-yl, thiophene-2-yl, furan-3-yl, furan-2-yl, pyridine-4-yl, pyridine-3-yl or pyridine-2-yl group wherein the substituents in these groups are those described later with reference to R^1 to R^5 in general formula (2):

(2)



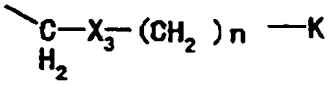
wherein R^1, R^2, R^3, R^4 and R^5 may be the same or different from each other and each represent hydrogen atom, a halogen atom, hydroxyl group, carboxyl group, amino group, cyano group, nitro group, a lower alkyl group, a lower alkoxyl group, a lower alkylamino

group, a lower alkylthio group, a lower alkanoyl group, a lower alkoxycarbonyl group, a hydroxy-lower alkyl group, a hydroxy-lower alkoxyl group, a hydroxy-lower alkenyl group, a halogeno-lower alkyl group, a halogeno-lower alkoxyl group, an amino-lower alkyl group, an amino-lower alkoxyl group, an amino-lower alkenyl group, a carboxy-lower alkyl group, a carboxy-lower alkoxyl group, a carboxy-lower alkenyl group, [an aryl-lower alkoxyl] a benzyloxy group, [or an aroyl] a benzoyl, or a pyridylcarbonyl group,

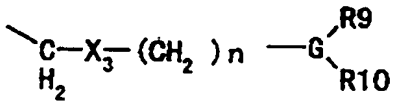
C represents hydrogen atom, a lower alkyl group, a hydroxy-lower alkyl group, [an aryl-lower alkyl] a benzyl group, a [heteroaryl-lower alkyl] pyridylmethyl group, an amino-lower alkyl group or a carboxy-lower alkyl group;

D represents hydrogen atom, a lower alkyl group, dimethoxymethyl group, cyano group, [an aryl-lower alkyl] a benzyl group, a [heteroaryl-lower alkyl] pyridylmethyl group, a hydroxy-lower alkyl group, a halogeno-lower alkyl group, an amino-lower alkyl group, a carboxy-lower alkyl group or a group of the following formula (5) or (6):

(5)



(6)



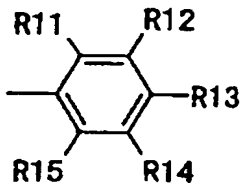
wherein X_3 represents O, S or N-$R^{8'}$, n represents an integer of 0 to 6, K in general formula (5) represents hydrogen atom, a halogen atom, hydroxyl group, carboxyl group, amino group, cyano group, nitro group, azido group, a substituted or unsubstituted [aryl] phenyl group or a substituted or unsubstituted heteroaryl group, wherein said heteroaryl group

is selected from the group consisting of a pyridyl group, a furyl group, and a thienyl group and wherein the substituents in these groups are those described later with reference to R^1 to R^5 in general formula (2), G in the formula (6) represents N or C-H, wherein $R^{8'}$ to R^{10} may be the same or different from each other, and they each represent hydrogen atom, a linear, branched or cyclic, saturated or unsaturated hydrocarbon group having 1 to 6 carbon atoms, a substituted or unsubstituted [aryl] phenyl group, a substituted or unsubstituted heteroaryl group, wherein said heteroaryl group is selected from the group consisting of a pyridyl group, a furyl group, and a thienyl group, a hydroxy-lower alkyl group, a hydroxy-lower alkenyl group, a halogeno-lower alkyl group, a halogeno-lower alkenyl group, an amino-lower alkyl group, an amino-lower alkenyl group, a carboxy-lower alkyl group, a carboxy-lower alkenyl group, an [aryl-lower alkyl] benzyl group, [an aryl-lower alkenyl group,] a [heteroaryl-lower alkyl] pyridylmethyl group, a [heteroaryl-lower alkenyl group,] a cyano-lower alkyl group or a cyano-lower alkenyl group, and the chains may contain a hetero atom wherein the substituents in the substituted phenyl, pyridyl, furyl and thienyl groups of $R^{8'}$ are halogen atoms, alkyl groups, and alkoxyl groups and the substituents in the substituted phenyl, pyridyl, furyl and thienyl groups of R^9 and R^{10} are those described later with reference to R^1 to R^5 in general formula (2), or R^9 and R^{10} may together form a ring [which may contain a hetero atom] selected from the group consisting of a cyclopentyl group, a cyclohexyl group, a piperidine-1-yl group, a piperidine-4-yl group, a pyrrolidine-1-yl group, a pyrrolidine-3-yl group, a piperidinone-1-yl group, a pyrrolidinone-1-yl group, a piperazine-1-yl group and a morpholine-4-yl group;

E represents hydrogen atom [(], only when L represents oxygen atom and Y represents

an interatomic bond[])], a group of the following general formula (7), a substituted or unsubstituted heteroaryl group, wherein said heteroaryl is selected from the group consisting of a thiophene-3-yl group, a thiophene-2-yl group, a furan-3-yl group, a furan-2-yl group, a pyridine-4-yl group, a pyridine-3-yl group, a pyridine-2-yl group, and an imidazole-1-yl group, cyclopentyl group, cyclohexyl group, pyrrolidinone-1-yl group or piperidinone-1-yl group wherein the substitutents in these heteroaryl groups are halogen atoms, alkyl groups, and alkoxyl groups, when E represents cyclopentyl group, cyclehexyl group, pyrrolidinone-1-yl group or piperidinane-1-yl group, Z is a group having the formula (Z_2):

(7)



wherein R^{11}, R^{12}, R^{13}, R^{14} and R^{15} may be the same or different from each other and each represent hydrogen atom, a halogen atom, hydroxyl group, carboxyl group, amino group, cyano group, nitro group, a lower alkyl group, a lower alkoxyl group, a lower alkylamino group, a lower alkylthio group, a lower alkanoyl group, a hydroxy-lower alkyl group, a hydroxy-lower alkoxyl group, a hydroxy-lower alkenyl group, a halogeno-lower alkyl group, a halogeno-lower alkoxyl group, an amino-lower alkyl group, an amino-lower alkoxyl group, an amino-lower alkenyl group, a carboxy-lower alkyl group, a carboxy-lower alkoxyl group, a carboxy-lower alkenyl group, [an aryl-lower alkyl] benzyl group, [an aryl-lower alkoxyl]

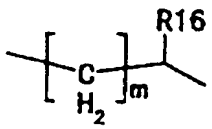
benzyloxy group, a lower alkoxycarbonyl group, [an aroyl] benzoyl, pyridylcarbonyl group, a substituted or unsubstituted [aryl] phenyl group, a substituted or unsubstituted heteroaryl group, wherein said heteroaryl group is selected from the group consisting of a pyridyl group, a furyl group, and a thienyl group, or [a saturated cyclic hydrocarbon having 3 to 8 carbon atoms, which may contain a hetero atom in the chain thereof and/or in the ring thereof,] cyclopentyl group, cyclohexyl group, piperidyl group, pyrrolidinyl group and piperadinyl group wherein the substituents in the substituted phenyl, pyridyl, furyl and thienyl groups are halogen atoms, alkyl groups, and alkoxyl groups,

X_1 represents an interatomic bond, $-CH_2-$, $-CH_2CH_2-$, -CH=CH- or -C≡C-,

L represents >N-F or oxygen atom [(], only when Z represents Z_1[)],

wherein F represents hydrogen atom or a lower alkyl group which may contain a hetero atom in the chain thereof, a hydroxy-lower alkyl group, an amino-lower alkyl group, a carboxy-lower alkyl group or a lower alkyloxycarbonyl-lower alkyl group,

Y represents an interatomic bond [(], only when L represents oxygen atom and E represents hydrogen atom[)], a saturated or unsaturated linear hydrocarbon group having 1 to 6 carbon atoms, which may contain a hetero atom in the group thereof, or a group of the following formula (8):

(8) 

wherein R^{16} represents hydrogen atom, a substituted or unsubstituted, saturated or unsaturated linear, branched or cyclic hydrocarbon group having 1 to 6 carbon atoms, a substituted or unsubstituted [aryl] phenyl group, a substituted or unsubstituted heteroaryl group, wherein said heteroaryl group is selected from the group consisting of a pyridyl group, a furyl group, and a thienyl group, a hydroxy-lower alkyl group, a hydroxy-lower alkenyl group, a halogeno-lower alkyl group, a halogeno-lower alkenyl group, an amino-lower alkyl group, an amino-lower alkenyl group, a carboxy-lower alkyl group, a carboxy-lower alkenyl group, [an aryl-lower alkyl] benzyl group, [an aryl-lower alkenyl group,] a [heteroaryl-lower alkyl] pyridylmethyl group, [a heteroaryl-lower alkenyl group,] a cyano-lower alkyl group or a cyano-lower alkenyl group, and the chains of R^{16} optionally contain a hetero atom, when Z is a group represented by the formula (Z_1), R^{16} is a substituted or [optionally substituted aryl] unsubstituted phenyl or a heteroaryl group, wherein said heteroaryl group is selected from the group consisting of a pyridyl group, a furyl group, and a thienyl group, and m represents an integer of 0 to 5 wherein the substituents in the substituted phenyl, pyridyl, furyl and thienyl groups are halogen atoms, alkyl groups, and alkoxyl groups.--

--6. (Amended) The dihydropyrimidine derivatives, tautomers thereof and pharmaceutically acceptable salts thereof according to claim 1, wherein Z represents Z_1, L represents >N-F, A represents a group of general formula (2), B_1, C and F each represent hydrogen atom, D represents a lower alkyl group, E represents a group of general formula (7), X_1 represents an interatomic bond and Y represents a group of general formula (8) wherein m represents an integer of 1 to 4 and R_{16} represents a substituted or unsubstituted [aryl] phenyl group.--

--11. (Amended) The dihydropyrimidine derivatives, tautomers thereof and pharmaceutically acceptable salts thereof according to claim 1, wherein Z represents Z_1, L represents >N-F, A represents a group of general formula (2), B_1, C and F each represent hydrogen atom, D represents a lower alkyl group, E represents a group of general formula (7), X_1 represents an interatomic bond and Y represents a group of general formula (8), wherein m represents an integer of 1 to 4 and R_{16} represents a substituted or unsubstituted [aryl] phenyl group, or a saturated or unsaturated hydrocarbon group having 3 or 4 carbon atoms.--

--17. (Amended) The dihydropyrimidine derivatives, tautomers thereof and pharmaceutically acceptable salts thereof according to claim 1, wherein Z represents Z_2, L represents >N-F, C represents hydrogen atom, A represents a group of general formula (2), E represents a group of general formula (7), F represents hydrogen atom, X_1 represents an interatomic bond and B_2 represents a substituted or unsubstituted [aryl] phenyl group or a substituted or unsubstituted heteroaryl group, wherein said heteroaryl group is selected from the group consisting of a pyridyl, a furyl, and a thienyl.--

--19. (Amended) The dihydropyrimidine derivatives, tautomers thereof and pharmaceutically acceptable salts thereof according to claim 1, wherein Z represents Z_2, L represents >N-F, C represents hydrogen atom, A represents a group of general formula (2), E represents a group of general formula (7), F represents hydrogen atom, X_1 represents an interatomic bond and Y represents a group of general formula (8), wherein m represents an integer of 1 to 4 and R_{16} represents a substituted or unsubstituted [aryl] phenyl group.--

--21. (Amended) The dihydropyrimidine derivatives, tautomers thereof and pharmaceutically acceptable salts thereof according to claim 1, wherein Z represents Z_2, L

represents >N-F, C represents hydrogen atom, A represents a group of general formula (2), D represents a group of general formula (6), wherein X_3 represents oxygen atom, n represents an integer of 2 or 3 and R_9 and R_{10}, bonded together to form a 5- to 7-membered ring together with G, E represents a group of general formula (7), F represents hydrogen atom, X_1 represents an interatomic bond and Y represents a group of general formula (8), wherein m represents an integer of 1 to 4 and R_{16} represents a substituted or unsubstituted [aryl] phenyl group, or an unsaturated hydrocarbon group having 3 or 4 carbon atoms.--

--38. (Amended) The method of Claim 33, wherein said disease is pain caused by spinal injury, pain caused by diabetes, pain caused by thromboangitis obliterans, postoperative pain, migraine or visceral pain.--

--41. (New)--